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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,485	07/28/1999	LEOPOLD FLOHE	29473/35834	6901

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/362,485	FLOHE ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-18* is/are pending in the application.

4a) Of the above claim(s) *2-8 and 10-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

FINAL REJECTION

Continued Prosecution Application

1. The request filed on December 24, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/362,485 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claim 1 is now under consideration. Claims 2-8 and 10-18 have been withdrawn. The arguments presented in paper no. 22, filed March 5, 2002, have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. **This action is FINAL.**

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

4. It is noted that applicant's express election made in the prior application carries over to the instant CPA, and that prosecution is being continued on the invention elected and prosecuted in the prior application. See *MPEP* 819. Accordingly, claims 2-8 and 10-18 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10, and confirmed the status of the claims on page 1 of paper no. 22. It is also noted that the restriction requirement was deemed proper and made final in the Office action of paper no. 11.

Claim Rejections - 35 USC § 112

5. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to a "diagnostic kit" comprising an "enzymatic test kit" and a nucleic acid. However, while the specification as originally filed teaches both the enzymatic test kit and the nucleic acid sequences set forth in the claim, the specification does not disclose a diagnostic kit comprising both of these components, as required by the claim. In fact, no kit comprising the nucleic acids of instant claim 1, alone or in combination with any other reagents, is disclosed in the specification. Further, the specification does not disclose any other product or entity that could be considered equivalent to the product of claim 1 (e.g., the specification does not refer to a container or similar structure including all the components now set forth in claim 1). Accordingly, the specification does not provide basis for the diagnostic kit of claim 1.

In the response of paper no. 22, applicant traverses the rejection on the grounds set forth below. Applicants' arguments have been thoroughly considered but are not persuasive for the reasons given.

First, the response argues that the specification at pages 31-33 discloses that some mycobacteria lacking AlaDH activity may be virulent, and states that "Thus, in order to determine the virulence of a mycobacterium, one of skill in the art must determine both the AlaDH enzyme activity and determine whether

AlaDH DNA is present in the mycobacterium." This argument has been thoroughly considered but is not persuasive. The specification does disclose that the "deletion of base 272" discussed on page 31 and referred to in the response correlates with the absence of AlaDH activity. However, the specification also indicates that slow growing mycobacteria having AlaDH activity are virulent, and that other strains lacking AlaDH activity may also be virulent (specification p. 33). The specification does not indicate that "to determine the virulence of a mycobacterium, one of skill in the art must determine both the AlaDH enzyme activity and determine whether AlaDH DNA is present," as stated in the response. In contrast (and as cited by the response), the specification clearly states at page 33 that "a slow-growing mycobacterium having positive AlaDH activity is virulent," indicating that the presence of AlaDH activity in a slow growing strain is alone indicative of virulence. Further, irrespective of what the specification may or may not teach regarding methods of determining whether mycobacteria are virulent, it remains that the kits of the instant claim are not disclosed in the specification. The instant rejection arises from the absence of a disclosure of kits comprising the components of claim 1, and the teachings at pages 31-33 do not disclose or otherwise provide basis for such a kit. Thus, applicants' arguments are not persuasive.

The response further argues that "the application as filed recites that '[t]he disclosure also includes all conceivable combinations of the individual features disclosed,'" referring to page 37, lines 6-7 of the specification. In response, it is again noted that (as discussed in, e.g., the Advisory Action of paper no. 17 and in

the Office action of paper no. 23) even if this general statement regarding "all conceivable combinations" were sufficient to provide basis for the combination of two particular compositions or products not actually disclosed in combination with one another in the specification, the specification in the instant case does not in fact disclose a kit comprising nucleic acids which might form a "combination" with the disclosed enzymatic test kit. Accordingly, the present claim does not constitute a "conceivable combination" of the features of the invention, as nucleic acids present in a kit, container, etc., were never disclosed.

The response also urges that original claim 14 provides basis for the invention of present claim 1. However, as discussed in paper nos. 17 and 23, claim 14 merely provides a further limitation of the type of sample to be "used" in different methods; the claim does not disclose that the two different methods may be combined, but merely indicates that the same type of sample may be employed in the two separate methods. Further, there is no disclosure in the specification of a single method in which all of the steps of these two methods are carried out or in which all of the reagents of the product of claim 1 are employed, etc. While the response asserts that "the application as filed most certainly disclosed a method in which the claimed combination of components is employed," the response does not cite any actual instance of this teaching in the specification. Further, it is again noted that irrespective of what the specification may or may not teach regarding methods of determining whether mycobacteria are virulent, etc., it remains that the kits of the instant claim are not disclosed in the specification. The instant rejection arises from the absence of a disclosure of

kits comprising the components of claim 1 , and original claim 14 does not disclose or otherwise provide basis for such a kit. Accordingly, this argument is not persuasive.

Finally, with respect to applicants' argument regarding an intended use recited in a claim preamble (citing *Rowe v. Dror*), it is noted that while the recitation "for the diagnosis of tuberculosis and other mycobacterial infections" in claim 1 does constitute an intended use, the requirement for a "kit" is a structural limitation, in that the claimed product must be present in a structure that would be considered by one of ordinary skill in the art to constitute a kit (e.g., a container, an enclosure, within packing materials, etc.). The instant specification does not disclose a kit comprising nucleic acids as required by claim 1; accordingly, basis for such a structure is lacking, and applicants' arguments are not persuasive.

Claim Rejections - 35 USC § 103

6. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al in view of Ahern.

Andersen et al teach the nucleotide sequence of the *M. tuberculosis* L-alanine dehydrogenase gene, which comprises each of the sequences set forth in instant SEQ ID Nos 11-25 (see Andersen et al, Figure 5). It is a property of the molecule taught by Andersen et al that it is a nucleic acid consisting of a sequence that is "hybridizable" with the particular sequences recited in claim 1 under the conditions required by the claim. Andersen et al further teach that L-alanine dehydrogenase activity may be identified by employing a stain comprising NAD, L-alanine, PMS, and NBT (p. 2318). Accordingly, Andersen et

al disclose methods for characterizing L-alanine dehydrogenase in which all the components set forth in claim 1 are employed. However, Andersen et al does not teach packaging NAD, L-alanine, PMS, and NBT into a kit, or teach a kit comprising this kit and their DNA molecule. Ahern teaches that pre-made reagents provided in kit form are convenient and save researchers time and money (see p. 3/5-4/5). In view of the teachings of Ahern, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the invention of Andersen et al so as to have packaged any or all of the reagents taught by Andersen et al into a kit. An ordinary artisan would have been motivated to have made such a modification in order to have provided the reagents needed to perform Andersen et al's methods to practitioners in a convenient format for the advantages of efficiency and cost-effectiveness.

In the response of paper no. 22, applicant traversed the rejection on the grounds set forth below. Applicants' arguments have been thoroughly considered but are not persuasive for the reasons given below.

It is first noted that the instant rejection states that Andersen et al disclose "methods" – not a single method – "for characterizing L-alanine dehydrogenase in which all the components set forth in claim 1 are employed." The response traverses the rejection on the following grounds. The response argues that "no motivation to select these particular methods from Andersen has been identified" and that "the examiner is impermissibly picking and choosing from the Andersen disclosure, using the applicants specification as a guide to impermissibly arrive at

these hindsight reconstruction of the claimed subject matter," citing *In re Mills*. This argument has been thoroughly considered but is not persuasive. The instant claim is not drawn to a method, but rather to a kit comprising particular components, all of which are disclosed by Andersen et al. Further, the claim recites the open transitional language "comprising," and is therefore not limited to, e.g., a specific combination of components with which unexpected results were obtained (and exclusive of other components). As set forth at pages 4-5 of paper no. 20, one would have been motivated to have packaged "any or all of the reagents taught by Andersen et al into a kit" in order to "have provided the reagents needed to perform Andersen et al's methods to practitioners in a convenient format for the advantages of efficiency and cost-effectiveness," as taught by the Ahern reference. Accordingly, Applicants' arguments are not persuasive.

The response further argues that "Andersen did not disclose a nucleic acid consisting of one of the expressly provided partial sequences" of the claim. In response, it is noted that the claim merely requires a nucleic acid consisting of a sequence "hybridizable" with one of the particular sequences under the recited conditions. The nucleic acid of Andersen et al clearly meets this requirement (in fact, applicant's specification exemplifies amplification of mycobacterial alanine dehydrogenase genes using conditions meeting the requirements of the claim). Further, with respect to applicants' argument that Andersen does not disclose the use of the reagents of the instant claim in a single method, it is again noted that the claim necessitates no such requirement, as it is drawn to a kit comprising

components, not to a method or, more particularly, to a single method employing each of those components. Thus, applicants' arguments are not persuasive.

7. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al in view of Ahern, as applied to claim 1, above, and further in view of Innis et al ("Optimization of PCRs" in *PCR Protocols: a Guide to Methods and Applications*, Innis, M.A. et al, eds., Academic Press, Inc., San Diego, 1990, pages 3-12).

This rejection applies to the claim to the extent that it may be limited to kits comprising one or more nucleic acids consisting of the particular sequences set forth in the claim. The combined references of Andersen et al and Ahern do not teach nucleic acids consisting of the recited sequences. However, Andersen et al disclose that alanine dehydrogenase is expressed in some species of mycobacteria but not others, and teach that this protein has "potential relevance....for virulence and/or protection" (p. 2317). Accordingly, Andersen et al provide motivation to one of ordinary skill in the art to study alanine dehydrogenase gene structure and expression in different mycobacterial species. Further, Andersen et al suggest performing "genetic manipulations" in mycobacteria in order to inactivate alanine dehydrogenase and "get more information on the role of the enzyme in the metabolism and virulence of *M. tuberculosis*" (p. 2322). Thus, Andersen et al provide motivation to clone the alanine dehydrogenase gene or portions thereof so as to, e.g., construct clones for use in inactivation by homologous recombination. Innis et al disclose that PCR may be used to rapidly amplify nucleic acid targets of interest from complex

mixtures for further study by, e.g., visualization, screening, or sequencing (p. 3). Innis et al further disclose that a variety of primers meeting the general criteria set forth on page 9 of Innis et al may be used as "efficient primers". In view of the teachings of Andersen et al and Innis et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the alanine dehydrogenase nucleic acid of Andersen et al so as to have prepared fragments or subsequences thereof for use as primers in PCR amplification of mycobacterial alanine dehydrogenase genes. An ordinary artisan would have been motivated to have made such a modification in order to have rapidly cloned and/or sequenced alanine dehydrogenase genes from mycobacteria for the advantage of rapidly determining and studying the structure and expression of those genes and/or rapidly preparing clones for use in homologous recombination, as suggested by Andersen et al. Further, given the teachings of Innis et al, any primers consisting of portions of a known target molecule sequence (e.g., portions of the sequence taught by Andersen et al) and meeting Innis et al's general guidelines for "efficient primers", including the sequences set forth in instant claim 1, would be obvious to one of ordinary skill in the art. The present claim is not limited to, e.g., a particular primer pair with which unexpected results were obtained. Absent a showing of unexpected results, any primers consisting of subsequences of a known gene sequence and meeting known criteria for PCR primers are considered to be functionally equivalent for, e.g., amplification of that gene, and it would have been obvious to one of ordinary skill to have prepared such primers for that purpose. It is further

noted that the claim as written is not limited to primers, but encompasses probes consisting of the particular sequences recited in the claim. Absent a showing of unexpected results with probes that consist of particular subsequences of a gene sequence known in the art (e.g., the L-alanine dehydrogenase gene sequence taught by Andersen et al which comprises each of SEQ ID NOs 11-25), such probes are also considered to be functionally equivalent for, e.g., detection of the gene, and it would have been obvious to one of ordinary skill in the art at the time the invention was made to have prepared fragments of the nucleic acids of, e.g., Andersen et al, because such fragments would have been useful as probes.

In the response of paper no. 22, applicant traversed the rejection on the same grounds set forth above. Accordingly, the response to those arguments applies equally herein. Further, with respect to applicants' argument that "Andersen did not disclose a nucleic acid consisting of one of the expressly provided partial sequences" of the claim, it is noted that the instant rejection did not make such an assertion. Rather, the Innis et al reference was cited for its guidance with respect to the preparation of primers for use in PCR (see p. 5-7 of paper no. 20). Applicant's arguments are not persuasive.

Conclusion

8. This is a CPA of applicant's earlier Application No. 09/362,485. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP

§ 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
March 5, 2003

CARLA J. MYERS
PRIMARY EXAMINER